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(54) Title: EXTENDED RELEASE ORAL DOSAGE COMPOSITION

(57) Abstract: A compressed bilayer solid composition comprising (a) an immediate release first layer comprising an anti-allergic effective amount of desloratadine and at least one pharmaceutically acceptable excipient and (b) a sustained release second layer comprising an effective amount of a nasal decongestant and a pharmaceutically acceptable sustained release agent wherein the composition contains less than about 2 % of desloratadine decomposition products is disclosed.

# EXTENDED RELEASE ORAL DOSAGE COMPOSITION

## BACKGROUND OF THE INVENTION

This invention relates to a bilayer sustained release oral dosage composition containing a nasal decongestant, e.g., pseudoephedrine in one layer and the non-sedating antihistamine, desloratadine in a second layer and having less than about 2% of desloratadine degradation products. The oral dosage compositions of this invention are useful for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions such as the common cold, as well as signs and symptoms associated with allergic and/or inflammatory conditions of the skin and airway passages such as dermatitis, allergic rhinitis, seasonal allergic rhinitis and nasal congestion, upper respiratory diseases, allergic rhinitis and nasal congestion.

Desloratadine, also called descarbethoxyloratadine, is disclosed in US Patent No. 4,659,716 as a non-sedating antihistamine useful as an anti-allergy agent . US Patent No. 5,595,997 discloses methods and compositions for treating seasonal allergic rhinitis symptoms using desloratadine.

U. S. Patent Nos. 4,990,535 and 5,100,675 disclose a twice-a-day sustained release coated tablet wherein the tablet coating comprises descarbethoxyloratadine and a hydrophilic polymer and polyethylene glycol, and the tablet core comprises acetaminophen, pseudoephedrine or a salt thereof, a swellable hydrophilic polymer and pharmaceutically acceptable excipients.

U. S. Patent No. 5,314,697 discloses an extended release tablet containing matrix core comprising pseudoephedrine sulfate and a coating comprising loratadine.

None of the prior art discloses the twice-a-day non-film-coated oral dosage composition of this invention.

The successful development of a formulation of a desloratadine-pseudoephedrine twice-a-day product would be desirable, but would require (1) achieving a release rate profile for pseudoephedrine component over an extended period of about twelve hours while maintaining the safety and effectiveness of

desloratadine, and (2) minimizing impurity formation due to the interaction between desloratadine and excipients in the pseudoephedrine layer that are incompatible with desloratadine.

It would be desirable for increased patient compliance to have a stable, extended release desloratadine-pseudoephedrine product substantially free of desloratadine impurities and additional polymorphic forms that is effective and safe when used on a twice-a-day or once-a-day basis for the treatment, management and/or mitigation of the signs and symptoms associated with the common cold, as well as allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as seasonal, allergic rhinitis and nasal congestion.

## SUMMARY OF THE INVENTION

We have found that desloratadine discolors and decomposes in the presence of excipients disclosed in the prior art. We have discovered that these problems are substantially solved (a) when the use of an acidic excipient in the desloratadine layer is avoided and when desloratadine is combined with a pharmaceutically acceptable carrier medium comprising a desloratadine protective amount of a pharmaceutically acceptable basic salt, or (b) when a desloratadine-protective amount of a pharmaceutically acceptable antioxidant is present in at least one layer and preferably at least one of said antioxidants is present in each layer of the bilayer tablet.

Thus, this invention provides a compressed bilayer solid composition comprising (1) an immediate release first layer comprising an anti-allergic effective amount of desloratadine and a desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt,or of a desloratadine-protective amount of at least one pharmaceutically acceptable antioxidant;and (2) a sustained release second layer comprising an effective amount of pseudoephedrine or a salt thereof, and a pharmaceutically acceptable sustained release agent, and optionally a desloratadine-protective amount of a pharmaceutically acceptable antioxidant.

Thus, in one preferred embodiment, this invention provides a compressed bilayer solid composition comprising (1) one layer- an immediate release first layer- comprising an anti-allergic effective amount of desloratadine and desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt, and (2) another layer-a sustained release second layer- comprising an effective amount of pseudoephedrine or a salt thereof, and a pharmaceutically acceptable sustained release agent.

The pharmaceutical compositions of the present invention contain less than about 2.0% of desloratadine decomposition products such as N-formyldesloratadine (see Chart I) when such compositions are stored at 25°C and about 60% relative humidity for extended time periods, e.g., about 18 months.

In a preferred embodiment, this invention provides a compressed bilayer solid composition comprising:

(a) an immediate release first layer comprising:

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 2.5 |
| Corn starch | 11.0 |
| Dibasic calcium phosphate dihydrate | 53.0 |
| Microcrystalline cellulose | 30.22 |
| Talc | 3.0 |
| FD&C Blue dye No. 2 Aluminium Lake 5627 | 0.28 |
| **TOTAL IN FIRST LAYER** | 100.00 |

and

(b) a second sustained release second layer comprising:

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate | 120.0 |
| Hydroxypropyl Methylcellulose | 105.0 |
| Microcrystalline cellulose | 100.0 |
| Povidone | 18.0 |
| Silicon Dioxide | 5.0 |
| Magnesium stearate | 2.0 |
| **TOTAL IN SECOND LAYER** | 350.0 |

The above-listed preferred compressed bilayer composition contains less than about 2.0% of desloratadine decomposition products such as N-formyl-desloratadine(see Chart I) when such compositions are stored at 25°C and about 60% relative humidity for extended time periods of about18 months.

Thus, in another preferred embodiment, the present invention also provides a compressed bilayer solid composition comprising (1) an immediate release first layer comprising an anti-allergic effective amount of desloratadine and a desloratadine-protective amount of at least one pharmaceutically acceptable antioxidant;and (2) a sustained release second layer comprising an effective amount of pseudoephedrine or a salt thereof, a pharmaceutically acceptable sustained release agent, and a desloratadine-protective amount of a pharmaceutically acceptable antioxidant.The above-listed preferred compressed bilayer composition contains less than about 2.0% of desloratadine decomposition products such as N-formyldesloratadine (see Chart I) when such compositions are stored at 25°C and about 60% relative humidity for extended time periods of about 18 months.

The present invention provides a compressed bilayer solid composition comprising (a) an immediate release first layer comprising an anti-allergic effective

amount of desloratadine and at least one pharmaceutically acceptable excipient and (b) a sustained release second layer comprising an effective amount of a nasal decongestant and a pharmaceutically acceptable sustained release agent. In a preferred embodiment, the compressed bilayer solid composition contains less than about 2.0% of desloratadine decomposition products such as N-formyl desloratadine after storage for about 18 months,and wherein at least about 80% of the desloratadine dissolves in 0.1N HCl at 37°C in about 45 minutes.

In another preferred embodiment, the present invention also provides a compressed bilayer solid composition comprising (1) an immediate release first layer comprising 5 mg of desloratadine and desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt ,and (2) a sustained release second layer comprising 120 mg of pseudoephedrine sulfate, and a pharmaceutically acceptable sustained release agent. This preferred composition provides a 24-hr dose of desloratadine and a 12-hr dose of pseudoephedrine sulfate.

Thus, the present invention also provides a method of treating and/or preventing allergic and inflammatory conditions of the upper and lower airway passages and skin which comprises administering to a patient in need of such treating an effective amount of a compressed bilayer solid composition of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

During the course of development of the compositions of the present invention, desloratadine was found to be unstable and to discolor when stored in combination with various excipients such as those disclosed in U.S. Patent No. 5,314,697 as part of the matrix core containing pseudoephedrine sulfate. The excipients causing discoloration and instability of desloratadine include acidic excipients having a pH of less than 7 in water such as organic acids, such as stearic acid, povidone, crospovidone as well as the hydroxycarboxylic acid, ascorbic acid, and carbonyl-containing materials such as lactose, and ethylcellulose and hydroxylpropyl methylcellulose. Binders like povidone and polymers such as hydroxypropyl methylcellulose are useful as a polymer matrix for

the sustained release of the pseudoephedrine sulfate from the inner polymer matrix core.

We also discovered that metal ions catalyzed were involved in the formation of desloratadine degradation products.

We have discovered two solutions to inhibit and/or prevent formation of desloratadine degradation products. In one preferred embodiment, a desloratadine-protective amount of a pharmaceutically acceptable anti-oxidant should be present in at least one of the bilayers, preferably one of said antioxidant in each layer.

In a second preferred embodiment, we also discovered that it is possible to prepare a bilayer tablet containing desloratadine in an immediate release first layer in intimate contact with a sustained release second layer containing a nasal decongestant and excipients incompatible with desloratadine by incorporating a desloratadine protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt into the immediate release desloratadine layer.

The term " in intimate contact" as used herein in reference to the two layer forming the bilayer tablet means that there is with no film interface between the two layers.

The term "pharmaceutically acceptable antioxidant" as used herein in reference to desloratadine (formula I in the Chart ) means a pharmaceutically acceptable chelating agent that protects desloratadine from the formation of degradation products including, but not limited to those of the formulas II-V listed in the Chart ,e.g.,N-formyl-desloratadine or N-formyl DL(formula II in the Chart ), N-hydroxylamine of DL (formula V in the Chart ) N-oxide of DL(formula IV in the Chart ), and the 3'-hydroxyl N-oxide of DL(formula III in the Chart ). The structures listed in the Chart were determined by standard physiochemical techniques, e.g., LC-MS, and LC-NMR.

Typically suitable pharmaceutically acceptable antioxidants for DL are pharmaceutically acceptable chelating agents such as those disclosed in "Chelating Agents", pages 764-794, Vol. 5 of KIRTH-OTHMER, ENCYCLOPEDIA OF CHEMICAL TECHNOLOGY, 4th Edition, 1993, John Wiley & Sons Inc., NY, and preferably including, but not limited to, hydroxycarboxylic acids, such as tartaric acid, citric acid and gluconic acid, and pharmaceutically acceptable salts thereof, aminocarboxylic acids such as edetic acid (ethylenediamine tetraacetic acid) and pharmaceutically acceptable

salts thereof such as edetate calcium disodium, edetate disodium, edetate trisodium, and edetate tetrasodium. Edetate disodium and citric acid are the preferred pharmaceutically acceptable antioxidants. Use of the hydroxycarboxylic acid, ascorbic acid, is to be avoided

The desloratadine protective amount of a pharmaceutically acceptable antioxidant in the DL immediate release layer is in the range of about 0.1% to about 10% by weight, preferably about 1% to 8% or about 1% to about 6%, more preferably about 4% to about 8%, or about 4% to about 6%, or most preferably about 5% to about 6%. The desloratadine protective amount of a pharmaceutically acceptable antioxidant in the PES sustained release layer is in the range of 0% to about 10%, preferably about 0.1% to about 10%, or about 0.1% to about 3%, more preferably about 1 to about 2%, and most more preferably about 1.0%. In a preferred embodiment of the present invention, about 1.0% by weight of a pharmaceutically acceptable antioxidant, e.g., edetate disodium, is present in the PES sustained release layer. In another preferred embodiment, about 6% by weight of a mixture of two pharmaceutically acceptable antioxidants, e.g., edetate disodium and citric acid, are present in the DL immediate release layer in a ratio of about 5:1 to about 1:5, preferably about 5:1, and about 1% of a pharmaceutically acceptable antioxidant, e.g., edetate disodium, is present in the sustained release layer. In another preferred embodiment, about 5% by weight of one pharmaceutically acceptable antioxidant, e.g., edetate disodium, is present in the DL immediate release layer.

In other preferred embodiments, about 5.0 mg (a 24-hour supply) of DL is present in the DL immediate release layer, and 120 mg (a 12-hour supply) of the nasal decongestant pseudoephedrine sulfate is present in the sustained release layer(see Examples 4,5&6). In one preferred embodiment, the dibasic phosphate salt preferably dibasic calcium phosphate dihydrate is present in the DL immediate release layer and no pharmaceutically acceptable antioxidant is present in either layer (see Example 4). In another preferred embodiment, 5.0 mg (a 24-hour supply) of DL and about 0.1 to about 10% of at least one antioxidant is present in the DL immediate release layer, preferably about 4% to about 6% of a mixture of two antioxidants, e.g., edetate disodium and citric acid, in a ratio of 5:1 to 1:1, preferably in a ratio of 5:1, and about 0.1% to about 10% preferably about 0.1% to about 5%, more preferably about 0.1% to

about 3%, most more preferably about 1.0% of an antioxidant, e.g., edetate disodium, is present in the PES sustained release layer(see Examples 5&6).

The desloratadine was found to have an acceptable immediate release profile from the second layer (80% release in 0.1N HCl in less than about 45 min.) and contain less than about 2% of desloratadine degration products even after storage for at least 18 months at 25° C and about 60% relative humidity ("RH").

The phrase "allergic and inflammatory conditions of the skin and airway passages" means those allergic and inflammatory conditions and symptoms found on the skin and in the upper and lower airway passages from the nose to the lungs. Typical allergic and inflammatory conditions of the skin and upper and lower airway passages include seasonal and perennial allergic rhinitis, non-allergic rhinitis, asthma including allergic and non-allergic asthma, sinusitis, colds (in combination with a NSAID, e.g., aspirin ibuprofen or APAP) and/or a decongestant e.g. pseudoephedrine), dermatitis, especially allergic and atopic dermatitis, and urticaria and symptomatic dermographism as well as retinophathy, and small verssel diseases, associated with diabetes mellitus.

The amount of desloratadine effective for treating or preventing allergic and inflammatory conditions of the skin and upper and lower airway passages will vary with the age, sex, body weight and severity of the allergic and inflammatory condition of the patient. Typically, the amount of desloratadine effective for treating or preventing such allergic and inflammatory conditions is in the range of about 2.5 mg/day to about 60 mg/day, preferably about 2.5 mg/day to about 20 mg/day, or about 4.0 mg/day to about 15 mg/day, or about 5.0 mg/day to about 10 mg/day, more preferably about 5.0 mg/day to about 10.0 mg/day, and most preferably about 5.0 mg/day in one dose or in two divided doses of 2.5 mg/dose.

Desloratadine is a non-sedating long acting histamine antagonist with potent selective peripheral H1-receptor antagonist activity. Following oral administration, loratadine is rapidly metabolized to descarboethoxyloratadie or desloratadine, a pharmacologically active metabolite. *In vitro* and *in vivo* animal pharmacology studies have been conducted to assess various pharmacodynamic effects of desloratadine and loratadine. In assessing antihistamine activity in mice

(comparison of $ED_{50}$ value), desloratadine was relatively free of producing alterations in behavior alterations in behavior, neurologic or autonomic function. The potential for desloratadine or loratadine to occupy brain H1-receptors was assessed in guinea pigs following i.p. administration and results suggest poor access to central histamine receptors for desloratadine or loratadine.

In addition to antihistaminic activity, desloratadine has demonstrated anti-allergic and anti-inflammatory activity from numerous *in vitro* and *in vivo* tests. These *in vitro* tests (mainly conducted on cells of human origin) have shown that desloratadine can inhibit many events in the cascade of allergic inflammation. These anti-inflammatory effects for desloratadine are independent of the H1-antagonist effect of desloratadine and include:

- The release of inflammatory mediators histamine, truptase, leukotriene and prostaglandin D2 from mast cells;
- The release of inflammatory cytokines including IL-4, IL-6, IL-8 and IL-13;
- The release of the inflammatory chemokines such as RANTES (regulated upon activation, normal T cell expressed and presumably secreted);
- Superoxide anion production of polymorphonuclear neutrophils;
- The expression of cell adhesion molecules such as intracellular adhesion molecules (ICAM-1) and P-selection in endothelial cells; and
- Eosinophil migration and adhesion

In vivo studies also suggest that an inhibitory effect of desloratadine on allergic bronchospasm and cough can also be expected.

The clinical efficacy and safety of desloratadine has been documented in over 3,200 seasonal allergic rhinitis patients in 4 double-blind, randomized clinical trials. The results of these chemical studies demonstrated the efficacy of desloratadine in the treatment of adult and adolescent patients with seasonal rhinitis.

The nasal decongestants useful in the present invention include phenylpropanolamine, phenylephrine and and pseudoephedrine. Pseudoephedrine as well as pharmaceutically acceptable acid additional salts, e.g., those of HCl or $H_2SO_4$, is a sympathomimetic drug recognized by those skilled in the art as a safe therapeutic agent effective for treating nasal congestion and is commonly administered orally and

concomitantly with an antihistamine for treatment of nasal congestion associated with allergic rhinitis. The use of pseudoephedrine as a nasal decongestant in the present invention is preferred; the use of about 120 mg pseudoephedrine sulfate in the extended release layer is more preferred.

In the course of development of the compressed bilayer oral dosage composition of this invention, it was discovered that the selection of the polymers for the extended release layer was critical to achieve the desired extended release period of at least 12 hours,for pseudoephedrine sulfate. For example, the use of hydroxypropyl methylcellulose 4,000 cps or 15,000 cps as polymers in the matrix core did not provide this more preferred extended release period of at least 16 hours for dose of pseudoephedrine sulfate. We discovered that only by selecting for inclusion into the matrix core of specific weight ratios of three specific polymers was the desired pseudoephedrine release profile achieved. Only by combining (1) about one part by weight, preferably 1.05 parts by weight of hydroxypropyl methylcellulose 2208 USP, 100,000 cps with (2) about one part by weight, preferably 1.0 parts by weight of microcrystalline cyellulose together with (3) about 0.15-0.20 part by weight., preferably 0.17-0.18 parts by weight of povidone (per 1.05 parts by weight of hydroxypropyl methylcellulose) as a secondary binder was the more preferred extended release profile of at least 12 hours for pseudoephedrine sulfate from the extended release layer. The extended release layer also contains specific amounts of silicon dioxide as a glidant and magnesium stearate as a lubricant. The tablet hardness 20 ± 4 Strong-Cobb Units (SCU) is not greatly affected by the higher level of lubricant (6mg/tablet) but it is preferred to maintain the lubricant level at 1/9 part by weight of lubricant to one part by weight of povidone as secondary binder.

The term "lubricant' as used herein refers to a substance added to the dosage form to enable the dosage form, e.g., a tablet, after it has been compressed to release from the mold or die.

Suitable lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and the like. Preferably, magnesium stearate or talc is used.

The term "glidants" as used herein refers to a substance, such as an anti-caking agent, which improves the flow characteristics of a powder mixture.

Suitable glidants include silicon dioxide and talc. Preferably, silicon dioxide is used.

The term "binders" as used herein means any material that is added to pharmaceutical compositions to help hold such compositions together and release the medicament therefrom.

Suitable binders are selected those found in NF XVIII, page 2206 (1995) and include povidones, starches, celluloses, alginates, and gums and low molecular weight hydroxypropyl melthyl celluloses, especially hydroypropyl methyl celluose 2910.

The term "pharmaceutically acceptable water insoluble basic calcium, magnesium and aluminium salts" as used herein means the pharmaceutically acceptable carbonates, phosphates, silicates and sulfates of calcium, magnesium and aluminum or mixtures thereof. Typically suitable pharmaceutically acceptable basic salts include calcium sulfate anhydrous, hydrates of calcium sulfate, such as calcium sulfate dihydrate, magnesium sulfate anhydrous, hydrates of magnesium sulfate, dibasic calcium phosphate, dibasic calcium silicate, magnesium trisilicate, magnesium phosphate, aluminum silicate, and hydrates of magnesium phosphate, aluminum phosphate; and calcium phosphate is more preferred. The use of dibasic calcium phosphate dihydrate is most preferred.

The desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt is in the range of about 50-60% of the DL immediate release layer, and the w/w ratio of the pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt to DL is in the range of about 8:1 to about 40:1, more preferably is in the range of about 10:1 to about 20:1, and most preferably is in the range of about 10:1 to about 11:1.

In the preferred embodiment of the present invention wherein a desloratadine protective amount of a pharmaceutically acceptable antioxidant is present, the water insoluble basic calcium salt is not present in the immediate release layer containing desloratadine; in its place, at least one, preferably two pharmaceutically acceptable antioxidants are present, e.g., edetate sodium and citric acid and the amount of microcrystalline cellulose is increased. In addition, when the pharmaceutically acceptable antioxidant is used in place of the water insoluble basic calcium, magnesium or aluminum salt, the povidone in the sustained release layer is replaced by another

binder, preferably a low molecular weight hydroxypropyl methyl cellulose ("HPMC"), preferably HPMC 2910.

The oral dosage composition of this invention also provides a shelf life of up to 18 months so long as the tablets are stored in standard package at between 2° and 30° C in an ambient environment of 60% relative humidity.

In the preparation of the bilayer tablet, the sustained release layer is compacted first. The immediate release second layer is added on top and a compression force sufficient to form a bilayer tablet is applied in the range of 8-12 kilo Newtons, preferably about 9 kilo Newtons(kN).

The dried sustained release granulation is milled and blended with requisite amounts of silicon dioxide and magnesium stearate.In a preferred embodiment, a pharmaceutically acceptable blue dye containing EDTA as a chelating agent is incorporated into the immediate release desloratadine layer. Use of a pharmaceutically acceptable blue dye, e.g. FD& C blue dye No. 2 Aluminum Lake 5627 is preferred.

## EXAMPLE I

This example illustrates preparation of the preferred oral dosage composition of this invention. The ingredients and specific amounts thereof are listed below.

A. **Method of Manufacture of the Immediate Release Layer**

1. Prepare starch paste by dispersing the paste portion of corn starch into purified water in a suitable container equipped with an agitator.

2. While mixing, heat the contents to approximately 95°C and maintain the temperature for approximately 30 minutes.

3. After Step 2 is completed, add an additional purified water and allow the starch paste to cool to approximately 50°C.

4. While mixing, add desloratadine to the starch paste. Continue mixing during the granulation step.

5. Pass the FD&C blue No. 2 aluminum lake containing EDTA as a chelating,e.g., Spectra Spray Med Blue, with the required amount of dibasic calcium phosphate through a suitable sieve or mill.

6. Charge to a suitable fluid bed processing bowl the remaining dibasic calcium phosphate dihydrate, the milled material from Step 5, a portion of the corn starch, and a portion of microcrystalline cellulose. Place the processing bowl into the fluid bed processor.

7. Fluidize the powder bed until the product temperature reaches approximately 29°C.

8. Begin granulating the powder by pumping the starch paste from Step 4 into the fluidized bed at a suitable spray rate and a bed temperature of approximately 22°C.

9. Continue to dry the granulation at an inlet air temperature of approximately 60°C until a final loss on drying (LOD) of 2% or less is achieved.

10. Pass the dried granulation through a suitable sieve or mill.

11. Charge the granulation to a suitable blender and add the requisite amounts of the remaining portion of microcrystalline cellulose, corn starch, and talc. Blend for 5 minutes.

**B. Manufacture of Sustained Release Mix:**

1. Charge purified water and alcohol to a suitable container equipped with an agitator.

2. Dissolve povidone in the water/alcohol mixture. Continue mixing for a minimum of 10 minutes.

3. Mix hydroxypropyl methylcellulose, pseudoephedrine sulfate and microcrystalline cellulose in a suitable granulator.

4. Granulate the mix with the povidone solution, using additional water/alcohol mixture if necessary to achieve the appropriate granulation consistency.

5. Dry the wet granulation at approximately 50°C in a suitable dryer until the loss on drying (LOD) is between 1% and 3%.

6. Pass the dried granulation through a suitable sieve or mill.

7. Charge the milled granulation to a suitable blender.

8. Pass the silicon dioxide through a No. 30 mesh screen into the blender.

9. Blend the requisite amount of screened silicon dioxide with the granulation for approximately 10 minutes in a suitable blender.

10. Pass the magnesium stearate through a No. 30 mesh screen.

11. Blend the requisite amount of screened magnesium stearate with the mix from Step 9 for 5 minutes.

**C. Compression:**

Compress the two blends to specifications as bilayer tablets using a suitable double-lay r tablet press using a compression force of 9k Newtons. Compress the sustained release layer first.

- Tablet Weight: 450 mg± 5%
  - Sustained release layer: 350 mg± 5%
  - Immediate release layer: 100 mg ± 5%
- Hardness: 20 ± 4 SCU (Strong Cobb units)

The following bilayer tablet was prepared using the above procedure.

**Desloratadine Immediate Release Layer:**

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 2.5 |
| Corn Starch NF/Ph.Eur. | 11.0 |
| Dibasic Calcium Phosphate Dihydrate USP/Ph.Eur. | 53.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 30.22 |
| Talc USP/Ph.Eur. | 3.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.28 |
| Water Purified USP/Ph.Eur. | qs |
| **TOTAL** | 100.00 |

and

**Pseudoephedrine Sulfate Sustained Release Layer**

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose USP/Ph.Eur. | 105.0 |
| Microcrystalline Cellulose 2208, 100,000cpsNF/Ph.Eur./JP | 100.0 |
| Povidone USP/Ph.Eur./JP | 18.0 |
| Silicon Dioxide NF | 5.0 |

| | |
|---|---|
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.0 |
| Water Purified USP/Ph.Eur. | --- |
| Alcohol USP/3A Alcohol | --- |
| **TOTAL** | 350.0 |
| **TOTAL TABLET** | 450.0 |

Hardness: 20 ± 4 SCU (Strong Cobb units)

**EXAMPLE 2**

The procedure of Example 1 was used; edetate disodium was used in place of the dibasic calcium salt and the amount of microcrystalline cellulose in the DL layer was increased. Edetate disodium was used in the sustained release layer and hydroxypropyl methylcellulose 2910 was used in place of povidone.

**Desloratadine Immediate Release Layer:**

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 2.5 |
| Corn Starch NF/Ph.Eur. | 8.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 71.35 |
| Edetate Disodium | 5.0 |
| Talc USP/Ph.Eur. | 3.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.15 |
| Water Purified USP/Ph.Eur. | --- |
| **TOTAL** | 100.00 |

and

**Pseudoephedrine Sulfate Sustained Release Layer**

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose 2208,USP/Ph.Eur. | 105.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 103.5 |

| | |
|---|---|
| Edetate Disodium | 3.5 |
| Hydroxypropyl Methylcellulose 2910 USP/Ph.Eur./JP | 10.5 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.5 |
| Water Purified USP/Ph.Eur. | --- |
| Alcohol USP/3A Alcohol | --- |
| **TOTAL** | 350.0 |
| **TOTAL TABLET** | 450.0 |

Hardness: 20 ± 4 SCU (Strong Cobb units)

## EXAMPLE 3

The procedure of Example 2 was used, but I mg of citric acid was added to the DL layer and .the amount of microcrystalline cellulose was decreased by 1 mg.

**Desloratadine Immediate Release Layer:**

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 2.5 |
| Corn Starch NF/Ph.Eur. | 18.0 |
| Edetate Disodium | 5.0 |
| Citric Acid | 1.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 70.35 |
| Talc USP/Ph.Eur. | 3.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.15 |
| Water Purified USP/Ph.Eur. | --- |
| **TOTAL** | 100.00 |

And **Pseudoephedrine Sulfate Sustained Release Layer**

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose 2208,100,000cps | |

| | |
|---|---|
| USP/Ph.Eur. | 105.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 103.5 |
| Edetate Disodium | 3.5 |
| Hydroxypropyl Methylcellulose 2910 | 10.5 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.5 |
| Water Purified USP/Ph.Eur. | --- |
| Alcohol USP/3A Alcohol | --- |
| **TOTAL** | 350.0 |
| **TOTAL TABLET** | 450.0 |

Hardness: 20 ± 4 SCU (Strong Cobb units)

**EXAMPLE 4**

The procedure of Example 1 was used. The bilayer tablet of Example 1 was modified by including 5.0 mg of desloratadine in the immediate release layer-(a 24 hour dose)-with the appropriate changes in amounts of the other ingredients and using the 12-hr dose pseudoephedrine sustained release layer of Example 1.

Hardness:20 ± 4 SCU (Strong Cobb units)

**Desloratadine Immediate Release Layer:**

| **INGREDIENT** | **mg/composition** |
|---|---|
| Desloratadine, micronized | 5.0 |
| Corn Starch NF/Ph.Eur. | 11.0 |
| Dibasic Calcium Phosphate Dihydrate USP/Ph.Eur. | 53.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 27.72 |
| Talc USP/Ph.Eur. | 3.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.28 |
| Water Purified USP/Ph.Eur. | --- |
| **TOTAL** | 100.00 |

and

**Pseudoephedrine Sulfate Sustained Release Layer**

| **INGREDIENT** | **mg/composition** |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |

| | |
|---|---|
| Hydroxypropyl Methylcellulose 2208,1000,00cps USP/Ph.Eur. | 105.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 100.0 |
| Povidone USP/Ph.Eur./JP | 18.0 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.0 |
| Water Purified USP/Ph.Eur. | --- |
| Alcohol USP/3A Alcohol | --- |
| **TOTAL** | 350.0 |
| **TOTAL TABLET** | 450.0 |

## EXAMPLE 5

The procedure of Example 1 was used and the bilayer tablet of Example 4 was modified by replacing the dibasic calcium phosphate dihydrate in the immediate release layer with 10 mg of edetate disodium and increasing the amount of microcrystalline cellulose by 2.7 mg. Hardness:20 ± 4 SCU (Strong Cobb units)

**Desloratadine Immediate Release Layer:**

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 5.0 |
| Corn Starch NF/Ph.Eur. | 36.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 142.7 |
| Edetate Disodium | 10.0 |
| Talc USP/Ph.Eur. | 6.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.30 |
| Water Purified USP/Ph.Eur. | ----- |
| **TOTAL** | 200.00 |

and

**Pseudoephedrine Sulfate Sustained Release Layer**

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose 2208,1000,00cps USP/Ph.Eur. | 105.0 |

| | |
|---|---|
| Microcrystalline Cellulose NF/Ph.Eur./JP | 103.5 |
| Hydroxypropyl Methylcellulose 2910 | 10.5 |
| Edetate Disodium | 3.5 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.5 |
| Water Purified USP/Ph.Eur. | — |
| Alcohol USP/3A Alcohol | — |
| **TOTAL** | 350.0 |
| **TOTAL Tablet Weight** | 550.0 |

## EXAMPLE 6

The bilayer tablet of Example 5 was modified by adding 2.0 mg of citric acid to the immediate release layer and decreasing the amount of microcrystalline cellulose by 2.7 mg and using the pseudoephedrine sustained release layer of Example 1. Hardness:20 ± 4 SCU (Strong Cobb units)

**Desloratadine Immediate Release Layer:**

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 5.0 |
| Corn Starch NF/Ph.Eur. | 36.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 140.7 |
| Edetate Disodium | 10.0 |
| Citric Acid | 2.0 |
| Talc USP/Ph.Eur. | 6.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.30 |
| Water Purified USP/Ph.Eur. | — |
| **TOTAL** | 200.00 |

And **Pseudoephedrine Sulfate Sustained Release Layer**

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose 2208,1000,00cps USP/Ph.Eur. | 105.0 |

| | |
|---|---|
| Microcrystalline Cellulose NF/Ph.Eur./JP | 103.5 |
| Hydroxypropyl Methylcellulose 2910 | 10.5 |
| Edetate Disodium | 3.5 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.5 |
| Water Purified USP/Ph.Eur. | --- |
| Alcohol USP/3A Alcohol | --- |
| **TOTAL** | 350.0 |
| **TOTAL Tablet Weight** | 550.0 |

The *in vitro* dissolution profile of the tablets of Examples 1-6 were measured in a stirred 0.1N HCl solution at 37°C (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37°C. The 80% of desloratadine in the immediate release layers was dissolved within the first 30 minutes and the total dose of pseudoephedrine sulfate in the sustained release layers was slowly released via erosion and dissolution mechanisms over a period of at least 12 hours.(with 30-45% in 1 hr, 50-605% in 2 hrs. and ≥80% in 6 hrs).

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine hydrochloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in a patient in need of such treating. The precise dosage and dosage regimen may be varied by the attending clinician in view of the teachings herein depending upon the requirements of the patient, e.g., the patient's age, sex and the severity of the allergic and/or inflammatory condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

While we have hereinabove presented a number of preferred embodiments of this invention by way of example, it is apparent that the scope of the invention is to be defined by the scope of the appended claims.

**WHAT IS CLAIMED IS:**

1) A compressed bilayer solid composition comprising (1) a first layer comprising an anti-allergic effective amount of desloratadine and a desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt, or of a desloratadine-protective amount of at least one pharmaceutically acceptable antioxidant;and (2) a second layer comprising an effective amount of pseudoephedrine or a salt thereof, and a pharmaceutically acceptable excipient, and optionally a desloratadine-protective amount of a pharmaceutically acceptable antioxidant.

2) A compressed bilayer solid composition comprising (1) a first layer comprising an anti-allergic effective amount of desloratadine and a desloratadine-protective amount of at least one pharmaceutically acceptable antioxidant;and (2) a second layer comprising an effective amount of pseudoephedrine or a salt thereof, a pharmaceutically acceptable excipient, and a desloratadine-protective amount of a pharmaceutically acceptable antioxidant.

3) A compressed bilayer solid composition comprising (1) a first layer comprising an anti-allergic effective amount of desloratadine and desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt, and (2) a second layer comprising an effective amount of pseudoephedrine or a salt thereof.

4) A compressed bilayer solid composition comprising (a) an immediate release first layer comprising an anti-allergic effective amount of desloratadine and at least one pharmaceutically acceptable excipient and (b) a sustained release second layer comprising an effective amount of a nasal decongestant and a pharmaceutically acceptable excipient, wherein the total amount of desloratadine degradation products is less than about 2%.

5) The compressed bilayer solid composition of any preceding claim wherein the first layer is an immediate layer and wherein the second layer is a sustained release layer containing a pharmaceutically acceptable sustained release agent.

6) The compressed bilayer solid composition of claim 5 wherein the nasal decongestant is pseudoephedrine, or a pharmaceutically acceptable salt thereof.

7) The compressed bilayer solid composition of any preceding claim wherein at least about 80% of the desloratadine dissolves in a 0.1N HCl solution at 37°C in about 45 minutes.

8) The compressed bilayer solid composition of any preceding claim wherein the amount of N-formyldesloratadine is less than about 0.5% after storage at 25°C and 60% relative humidity for an extended time period.

9) The compressed bilayer solid composition of claim 1 or 2 wherein about 0.1 % to about 10% of a pharmaceutically acceptable antioxidant is present in each layer.

10) The compressed bilayer solid composition of any preceding claim wherein the anti-allergic effective amount of desloratadine in the first layer is about 2.5 mg.

11) The compressed bilayer solid composition of any preceding claim wherein the anti-allergic effective amount of desloratadine in the first layer is about 5.0 mg.

12) The compressed bilayer solid composition of claim 1 or 2 wherein two pharmaceutically acceptable antioxidants are present in the desloratadine layer.

13) The compressed bilayer solid composition of claim 1 or 3 wherein an immediate release first layer comprises:

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 2.5 |
| Corn Starch | 11.0 |
| Dibasic Calcium Phosphate Dihydrate | 53.0 |
| Microcrystalline Cellulose | 30.22 |
| Talc | 3.0 |
| Dye FD+C Blue No. 2 Aluminium Lake | 0.28 |
| **TOTAL** | 100.00 |

and

and wherein an sustained release layer comprises

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate | 120.0 |
| Hydroxypropyl Methylcellulose | 105.0 |
| Microcrystalline cellulose | 100.0 |
| Povidone | 18.0 |
| Silicon Dioxide | 5.0 |
| Magnesium stearate | 2.0 |
| **TOTAL** | 350.0 |

14) The compressed bilayer solid composition of claim 1 or 3 wherein an immediate release first layer comprises:

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 2.5 |
| Corn Starch | 18.0 |
| Microcrystalline Cellulose | 70.35-71.35 |
| Edetate Disodium | 5.0 |
| Citric Acid | 0-1.0 |
| Talc | 3.0 |
| Dye FD+C Blue No. 2 Aluminium Lake | 0.28 |
| **TOTAL** | 100.00 |

and

and wherein an sustained release layer comprises:

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate | 120.0 |
| Hydroxypropyl Methylcellulose 2208 | 105.0 |
| Microcrystalline cellulose | 103.5 |
| Edetate Disodium | 3.5 |
| Hydroxypropyl Methylcellulose 2910 | 10.5 |
| Silicon Dioxide | 5.0 |
| Magnesium stearate | 2.0 |
| **TOTAL** | 350.0 |

15) A compressed bilayer solid composition comprising (1) a first layer comprising 2.5 or 5 mg of desloratadine and desloratadine-protective amount of a pharmaceutically acceptable water insoluble basic calcium, magnesium or aluminum salt, and (2) a second layer comprising 120 mg of pseudoephedrine or a salt thereof, and a pharmaceutically acceptable excipient.

16) A compressed bilayer solid composition comprising (1) a first layer comprising 2.5 mg or 5.0 mg of desloratadine and a desloratadine-protective amount of at least one pharmaceutically acceptable antioxidant;and (2) a second layer comprising 120 mg of pseudoephedrine or a salt thereof, a pharmaceutically acceptable excipient, and a desloratadine-protective amount of a pharmaceutically acceptable antioxidant.

17) The compressed bilayer solid composition of claim 15 or 16 wherein the amount of desloratadine in the first layer is about 2.5 mg.

18) The compressed bilayer solid composition of any preceding claim 15 or 16 wherein the amount of desloratadine in the first layer is about 5.0 mg.

19) The compressed bilayer solid composition of claim 1 or 3 wherein the immediate release first layer comprises:

**Desloratadine Immediate Release Layer:**

| INGREDIENT | mg/composition |
|---|---|
| Desloratadine, micronized | 5.0 |
| Corn Starch NF/Ph.Eur. | 11.0 |
| Dibasic Calcium Phosphate Dihydrate USP/Ph.Eur. | 53.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 27.72 |
| Talc USP/Ph.Eur. | 3.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.28 |
| Water Purified USP/Ph.Eur. | == |
| **TOTAL** | 100.00 |

and

**Pseudoephedrine Sulfate Sustained Release Layer**

| INGREDIENT | mg/composition |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose 2208,1000,00cps USP/Ph.Eur. | 105.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 100.0 |
| Povidone USP/Ph.Eur./JP | 18.0 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.0 |
| Water Purified USP/Ph.Eur. | — |

| | |
|---|---|
| Alcohol USP/3A Alcohol | --- |
| **TOTAL** | 350.0 |
| **TOTAL TABLET** | 450.0 |

20) The compressed bilayer solid composition of claim 1 or 2 wherein an immediate release first layer comprises:

**Desloratadine Immediate Release Layer:**

| **INGREDIENT** | **mg/composition** |
|---|---|
| Desloratadine, micronized | 5.0 |
| Corn Starch NF/Ph.Eur. | 36.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 140.7-142.7 |
| Edetate Disodium | 10.0 |
| Citric Acid | 0-2.0 |
| Talc USP/Ph.Eur. | 6.0 |
| Dye FD&C Blue No. 2 Aluminium Lake 5627 | 0.30 |
| Water Purified USP/Ph.Eur. | --- |
| **TOTAL** | 200.00 |

and

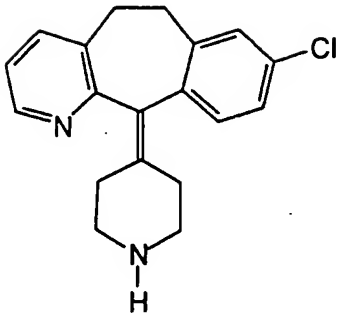
**Pseudoephedrine Sulfate Sustained Release Layer**

| **INGREDIENT** | **mg/composition** |
|---|---|
| Pseudoephedrine Sulfate USP | 120.0 |
| Hydroxypropyl Methylcellulose 2208, 1000,00cps USP/Ph.Eur. | 105.0 |
| Microcrystalline Cellulose NF/Ph.Eur./JP | 103.5 |
| Hydroxypropyl Methylcellulose 2910 | 10.5 |
| Edetate Disodium | 3.5 |
| Silicon Dioxide NF | 5.0 |
| Magnesium Stearate NF/Ph.Eur.JP(Non-Bovine) | 2.5 |

| | | |
|---|---|---|
| Water Purified USP/Ph.Eur. | | — |
| Alcohol USP/3A Alcohol | | — |
| | **TOTAL** | 350.0 |
| | **TOTAL Tablet Weight** | 550.0 |

21) The compressed bilayer solid composition of any preceding claim wherein the total amount of desloratadine degradation products is less than about 2%.

**CHART**

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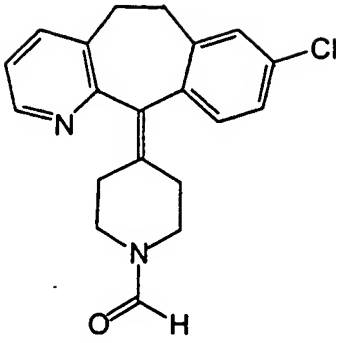


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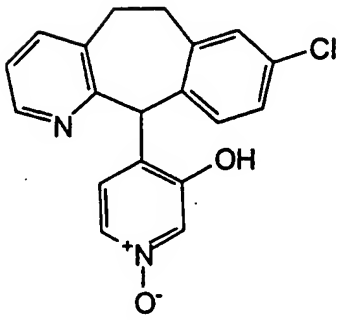
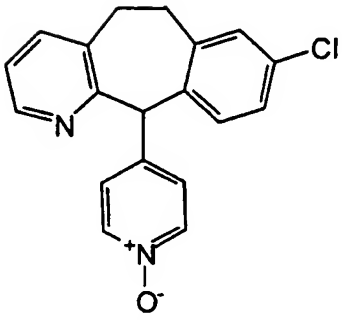
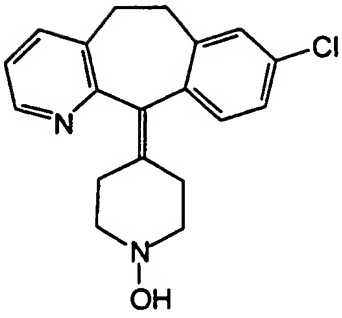



III




IV

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WO 01/45676 A3

(54) Title: EXTENDED RELEASE ORAL DOSAGE COMPOSITION

(57) Abstract: A compressed bilayer solid composition comprising (a) an immediate release first layer comprising an anti-allergic effective amount of desloratadine and at least one pharmaceutically acceptable excipient and (b) a sustained release second layer comprising an effective amount of a nasal decongestant and a pharmaceutically acceptable sustained release agent wherein the composition contains less than about 2 % of desloratadine decomposition products is disclosed.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/34404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K31/4545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 July 2001 | 12/07/2001 |

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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Benz, K |

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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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